

**Patent claims**

1. A method for biotechnologically producing valuable products in which a medium is fed to a bioreactor and subjected to a fermentation process and in which the valuable product is harvested, as filtered permeate and/or as concentrated retentate, by way of a downstream cross-flow filtration unit, and residues are supplied again to the bioreactor until harvesting as retentate, characterized in that, in addition to the medium, other substances can be fed to the bioreactor (1) in a controlled manner, in that the concentrated retentate and the permeate can be harvested in a controlled manner and in that the fermentation process and the filtration are regulated, in a manner in which they are matched to each other in an integrated system, by way of a control unit (6).

2. The method as claimed in claim 1, characterized in that the integrated system can be cleaned and sterilized in situ, with this being controlled by the control unit (6).

3. The method as claimed in claim 1 or 2, characterized in that recombinant proteins are produced as valuable products, with the permeate yielding a cell-free harvest and the retentate yielding a cell-contaminated harvest.

4. The method as claimed in one of claims 1 to 3, characterized in that the process proceeds while being conducted in a sequential and integrated manner.

5. The method as claimed in claim 3 or 4, characterized in that, in a batch phase (29), cells which are supplied to the bioreactor (1) adapt to the medium and, in a subsequent fed batch phase (30), the cells are propagated at a constant growth rate by means of feeding.

6. The method as claimed in one of claims 3 to 5, characterized in that, in a production phase (31), the induction of product formation, and the actual production of the recombinant proteins, take place by means of adding an inducing substance.

7. The method as claimed in claim 6, characterized in that the concentration of the inducing substance is measured by way of flow diffusion analysis and regulated by feeding from a second feed receptacle (3).

8. The method as claimed in one of claims 4 to 7, characterized in that, in a product harvesting phase (32), a part of the bioreactor (1) is harvested cell-free.

9. The method as claimed in claim 8, characterized in that, in a cell harvesting phase (33), cell mass in the retentate is harvested and this is followed by a medium refreshing phase (34) involving the feeding of medium (35).

10. The method as claimed in claim 9, characterized in that, after the medium refreshing phase (34), the cyclic process, in which, except in the product harvest, only the retentate stream, and not the permeate stream, is to flow, begins once again with the production phase (31).

11. The method as claimed in one of claims 3 to 10, characterized in that the recombinant proteins are produced using the yeast *Pichia pastoris*.

12. The method as claimed in claim 11, characterized in that methanol (36) is added, as inducing substance, to the medium (35) in the bioreactor (1) in order to induce the sequences of the cell protein.

13. The method as claimed in claim 12, characterized in that the methanol concentration is maintained at a constant level.

14. The method as claimed in one of claims 11 to 13, characterized in that glycerol (37) is fed in, in the fed batch phase (30) and/or in the production phase (31), for increasing production.

15. The method as claimed in one of claims 1 to 3 and 5 to 14, characterized in that the process proceeds while being conducted in a continuous and integrated manner.

16. The method as claimed in claim 15, characterized in that the production phase (31), the product harvesting phase (32) and the cell harvesting phase (33) proceed in parallel.

17. A device for biotechnologically producing valuable products, essentially comprising a bioreactor having an upstream first feed receptacle for a medium and a downstream cross-flow filtration unit whose permeate line is connected to a first harvest receptacle and whose retentate line leads back into the bioreactor, characterized in that at least one

second feed receptacle (3) containing an inducing substance is located upstream of the bioreactor (1), in that a second harvest receptacle (18) for a cell-contaminated harvest of the retentate is connected to the bioreactor (1) by way of a harvest line (19), and in that a control unit (6) is arranged for measuring and regulating the fermentation and filtration process.

18. The device as claimed in claim 17, characterized in that, for the purpose of measuring the concentration of the inducing substance in the bioreactor (1), the control unit (6) possesses an analytical system (24) which measures the concentration of the inducing substance by way of a sensor which is arranged in the bioreactor (1) and regulates the concentration of inducing substance in the bioreactor (1) by controlling a second feed pump (9) which is located upstream of the second feed receptacle (3).

19. The device as claimed in claim 18, characterized in that the analytical system (24) is in the form of a flow diffusion analysis (FDA) system.

20. The device as claimed in claim 17 or 18, characterized in that, for the purpose of measuring a cell concentration in the bioreactor (1), the control unit (6) possesses a second analytical system (27) which measures the cell concentration by way of a second sensor (28) which is arranged in the bioreactor (1) and regulates the cell concentration in the bioreactor (1) by controlling a harvest

pump (20) which is located upstream of the second harvest receptacle (18).

21. The device as claimed in one of claims 17 to 20, characterized in that, for the purpose of regulating the addition of medium to the bioreactor (1), a third regulator (44) is connected to a feed pump (8) by way of a weighing device (22) belonging to the bioreactor (1).